BIRTH DEFECT RISK FACTOR SERIES: 47,XXX

DESCRIPTION

Triple X syndrome was first described in 1959 (Jacobs et al., 1959). Triple X syndrome is a sex chromosomal abnormality that typically involves the presence of three X chromosomes, the resulting karyotype being 47,XXX. Mosaicism may occur where some cells in the body have triple X syndrome and other cells in the body have a different chromosome complement, with the most common karyotype being 47,XXX/46,XX.

Etiology

Triple X syndrome results from nondisjunction, usually in formation of the eggs or sperm, where one gamete ends with an extra X chromosome. Fertilization of an X egg by an XX sperm or an XX egg by an X sperm would result in a conceptus with triple X syndrome.

Approximately 90% of triple X syndrome cases are of maternal origin and 10% of paternal origin. Of the triple X syndrome cases of maternal origin, 70% result from nondisjunction in meiosis I (MI) (Jacobs and Hassold, 1995; MacDonald et al., 1994; May et al., 1990). Triple X syndrome resulting from maternal nondisjunction in MI is associated with advanced maternal age (MacDonald et al., 1994).

Phenotype

The clinical features of triple X syndrome are subtle and can be variable (Linden et al, 1996). Triple X syndrome is often not identified in infancy. Minor birth defects associated with triple X syndrome include hypertelorism, wide spaced nipples, brachycephaly, microcephaly (Buyse, 1990). Triple X syndrome cases typically have tall stature by adolescence and normal sexual development and puberty, are fertile, and have no or minor mental retardation but often have learning disabilities and may have problems with motor coordination (Linden et al, 1996).

Individuals with mosaic triple X syndrome often have a milder phenotype (Linden et al, 1996; Robinson et al., 1992; Salbenblatt et al., 1989). Generally, individuals with prenatally diagnosed triple X syndrome have fewer developmental problems than individuals with postnatally diagnosed triple X syndrome (Linden and Bender, 2002).

Prenatal diagnosis

Triple X syndrome may be prenatally diagnosed through cytogenetic analysis of cells obtained through such procedures as amniocentesis and chorionic villus sampling.

Fetal sex chromosomal abnormalities (47,XXX, 47,XXY, and 47,XYY) have been associated with increased nuchal translucency but normal maternal serum levels of free beta-human chorionic gonadotropin (hCG) and pregnancy-assisted plasma protein-A (PAPP-A) in the first trimester (Spencer et al., 2000; Sebire et al., 1998). However, first-trimester nuchal translucency and maternal serum screening are not routinely performed in the United States. One investigation found that the proportion of triple X syndrome cases in a population at increased risk of Down syndrome as a result of maternal serum screening was not greater than expected for the general population (Ryall et al., 2001). Moreover, fetuses with triple X syndrome typically do not have an abnormal ultrasound.

Thus cases of triple X syndrome will most likely be diagnosed prenatally incidental to a cytogenetic analysis for other reasons such as advanced maternal age.

PREVALENCE AND PREGNANCY OUTCOME

The prevalence of triple X syndrome has been reported to be 7.4-15.6/10,000 female births or 3.6-7.5/10,000 births (Table 1). Triple X syndrome has been reported in 6.5/10,000 amniocenteses (Horger et al., 2001).

The fetal death rate of triple X syndrome is not notably higher than that for conceptuses with normal chromosomes. It has been estimated that triple X syndrome occurs among 0.05% of clinically recognized pregnancies and that 94.4% of these conceptuses that are not electively terminated result in live births (Hassold and Jacobs, 1984).

Some triple X syndrome fetuses will be electively terminated when diagnosed prenatally (Table 2). Elective termination rates vary by study. Differences in termination rates between studies may reflect differences in time periods of the studies or differences in access to and/or use of prenatal diagnosis and elective termination. Termination rates for 47,XXX/46,XX are lower than for 47,XXX (Meschede et al., 1998).

Mortality/survival

One investigation reported that the infant mortality rate associated with all sex chromosome abnormalities increased during 1985-1997 (Lee et al., 2001).

Birth weight

One study reported the birth weight of triple X syndrome infants to be lower than the birth weight for controls (Jacobs et al., 1974).

Table 1. Prevalence per 10,000 births of 47,XXX

Reference	Location	Time period	Rate
Nielsen and Wohlert, 1991	Denmark	1969-1988	5.2, 10.6*
Hansteen et al., 1982	Norway	1978-1979	0.0
Buckton et al., 1980	Scotland	1976-1977	7.5, 15.6*
Hamerton et al., 1975	Canada	1970-1972	3.6, 7.4*
Jacobs et al., 1974	Scotland	1967-1972	4.3, 13.1*
Friedrich and Nielsen, 1973	Denmark	1969-1971	5.9, 12.3*

*rate per female births only

Table 2. Termination rates (%) of prenatally diagnosed triple X syndrome cases

Reference	termination rate (%)
Chaabouni et al., 2001	25
Horger et al., 2001	0
Sagi et al, 2001	67
Christian et al, 2000	65
Perrotin et al, 2000	33
Meschede et al, 1998	17
Verp et al, 1988	29
Verp et al, 1988 (review)	56
Holmes-Siedle et al, 1987	38
Holmes-Siedle et al, 1987 (review)	64
Nielsen and Videbec, 1984	66

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Sex

By definition, triple X syndrome occurs exclusively among females. However, cases of 47,XXX males have been reported (Scherer et al., 1989).

Parental age:

Increased risk of triple X syndrome is associated with advanced maternal age (Holmes-Siedle et al., 1987; Ferguson-Smith and Yates, 1984; Carothers et al., 1974).

Diabetes

One investigation reported a higher rate of triple X syndrome with maternal gestational diabetes (Moore et al., 2002).

Assisted Reproductive Technology (ART)

Triple X syndrome have been reported among infants conceived by intracytoplasmic sperm injection (ICSI) (Aboulghar et al., 2001).

Folate metabolism enzymes

No association has been reported between 47,XXY and 47,XXX cases combined and alleles for the folate metabolism enzymes methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) (Hassold et al., 2001).

REFERENCES

Aboulghar H, Aboulghar M, Mansour R, Serour G, Amin Y, Al-Inany H. A prospective controlled study of karyotyping for 430 consecutive babies conceived through intracytoplasmic sperm injection. Fertil Steril 2001;76:249-253.

Buckton KE, O'Riordan ML, Ratcliffe S, Slight J, Mitchell M, McBeath S, Keay AJ, Barr D, Short M. A G-band study of chromosomes in liveborn infants. Ann Hum Genet 1980;43:227-239.

Buyse ME, ed. Chromosome X, triplo-X. In: Birth Defects Encyclopedia. Cambridge, Massachusetts: Blackwell Scientific Publications, 1990:400.

Carothers AD, Collyer S, de Mey R, Frackiewicz A. Parental age and birth order in the aetiology of some sex chromosome aneuploidies. Ann Hum Genet 1974;41:277-287.

Chaabouni H, Chaabouni M, Maazoul F, M'Rad R, Jemaa LB, Smaoui N, Terras K, Kammoun H, Belghith N, Ridene H, Oueslati B, Zouari F. Prenatal diagnosis of chromosome disorders in Tunisian population. Ann Genet 2001;44:99-104.

Christian SM, Koehn D, Pillay R, MacDougall A, Wilson RD. Parental decisions following prenatal diagnosis of sex chromosome aneuploidy: a trend over time. Prenat Diagn 2000;20:37-40.

Ferguson-Smith MA, Yates JR. Maternal age specific rates for chromosome aberrations and factors influencing them: report of a collaborative European study on 52 965 amniocenteses. Prenat Diagn 1984;4:5-44.

Friedrich U, Nielsen J. Chromosome studies in 5,049 consecutive newborn children. Clin Genet 1973;4:333-343.

Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. Clin Genet 1975;8:223-243.

Hansteen IL, Varslot K, Steen-Johnsen J, Langard S. Cytogenetic screening of a new-born population. Clin Genet 1982;21:309-314.

Hassold TJ, Burrage LC, Chan ER, Judis LM, Schwartz S, James SJ, Jacobs PA, Thomas NS. Maternal folate polymorphisms and the etiology of human nondisjunction. Am J Hum Genet 2001;69:434-439.

Hassold TJ, Jacobs PA. Trisomy in man. Annu Rev Genet 1984;18:69-97.

Holmes-Siedle M, Ryynanen M, Lindenbaum RH. Parental decisions regarding termination of pregnancy following prenatal detection of sex chromosome abnormality. Prenat Diagn 1987;7:239-244.

Horger EO, Finch H, Vincent VA. A single physician's experience with four thousand six hundred genetic amniocenteses. Am J Obstet Gynecol 2001;185:279-288.

Jacobs PA, Hassold TJ. The origin of numerical

chromosome abnormalities. Adv Genet 1995;33:101-133.

Jacobs PA, Melville M, Ratcliffe S, Keay AJ, Syme J. A cytogenetic survey of 11,680 newborn infants. Ann Hum Genet 1974;37:359-376.

Jacobs PA, Baikie AG, Court-Brown WM, et al. Evidence for the existence of the human "super female." Lancet 1959;2:423-425.

Lee K, Khoshnood B, Chen L, Wall SN, Cromie WJ, Mittendorf RL. Infant mortality from congenital malformations in the United States, 1970-1997. Obstet Gynecol 2001;98:620-627.

Linden MG, Bender BG, Robinson A. Intrauterine diagnosis of sex chromosome aneuploidy. Obstet Gynecol 1996;87:468-475.

Linden MG, Bender BG. Fifty-one prenatally diagnosed children and adolescents with sex chromosome abnormalities. Am J Med Genet 2002;110:11-18.

MacDonald M, Hassold T, Harvey J, Wang LH, Morton NE, Jacobs P. The origin of 47,XXY and 47,XXX aneuploidy: heterogeneous mechanisms and role of aberrant recombination. Hum Mol Genet 1994;3:1365-1371.

May KM, Jacobs PA, Lee M, Ratcliffe S, Robinson A, Nielsen J, Hassold TJ. The parental origin of the extra X chromosome in 47,XXX females. Am J Hum Genet 1990;46:754-761.

Meschede D, Louwen F, Nippert I, Holzgreve W, Miny P, Horst J. Low rates of pregnancy termination for prenatally diagnosed Klinefelter syndrome and other sex chromosome polysomies. Am J Med Genet 1998;80:330-334.

Moore LL, Bradlee ML, Singer MR, Rothman KJ, Milunsky A. Chromosomal anomalies among the offspring of women with gestational diabetes. Am J Epidemiol. 2002;155:719-724.

Nielsen J, Videbech P. Diagnosing of chromosome abnormalities in Denmark. Clin Genet 1984;26:422-428.

Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 1991;87:81-83.

Perrotin F, Guichet A, Marret H, Potin J, Body G, Lansac J. Devenir prenatal des anomalies des chromosomes sexuels diagnostiquees pendant la grossesse. Analyse reptrospective de 47 cas. J Gynecol Obstet Biol Reprod (Paris) 2000;29:668-676.

Robinson A, Bender BG, Linden MG. Prognosis of prenatally diagnosed children with sex chromosome aneuploidy. Am J Med Genet 1992;44:365-368.

Ryall RG, Callen D, Cocciolone R, Duvnjak A, Esca R, Frantzis N, Gjerde EM, Haan EA, Hocking T, Sutherland G, Thomas DW, Webb F. Karyotypes found in the population declared at increased risk of Down syndrome following maternal serum screening. Prenat Diagn 2001;21:553-557.

Sagi M, Meiner V, Reshef N, Dagan J, Zlotogora J. Prenatal diagnosis of sex chromosome aneuploidy: possible reasons for high rates of pregnancy termination. Prenat Diagn 2001;21:461-465.

Salbenblatt JA, Meyers DC, Bender BG, Linden MG, Robinson A. Gross and fine motor development in 45,X and 47,XXX girls. Pediatrics 1989;84:678-682.

Scherer G, Schempp W, Fraccaro M, Bausch E, Bigozzi V, Maraschio P, Montali E, Simoni G, Wolf U. Analysis of two 47,XXX males reveals X-Y interchange and maternal or paternal nondisjunction. Hum Genet 1989;81:247-251.

Sebire NJ, Snijders RJ, Brown R, Southall T, Nicolaides KH. Detection of sex chromosome abnormalities by nuchal translucency screening at 10-14 weeks. Prenat Diagn 1998;18:581-584.

Spencer K, Tul N, Nicolaides KH.. Maternal serum free beta-hCG and PAPP-A in fetal sex chromosome defects in the first trimester. Prenat Diagn 2000;20:390-394.

Verp MS, Bombard AT, Simpson JL, Elias S. Parental decision following prenatal diagnosis of fetal chromosome abnormality. Am J Med Genet 1988;29:613-622.